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Date of mailing (day/month/year) 29 October 2001 (29.10.01)	
International application No. PCT/IN00/00094	**Applicant's or agent's file reference** PAN/CON/R/NIM
International filing date (day/month/year) 27 September 2000 (27.09.00)	**Priority date** (day/month/year) 28 September 1999 (28.09.99)
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1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   24 April 2001 (24.04.01)

   [ ] in a notice effecting later election filed with the International Bureau on:

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/22791 A2

(51) International Patent Classification: Not classified

(21) International Application Number: PCT/IN00/00094

(22) International Filing Date:
27 September 2000 (27.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1297/DEL/99 28 September 1999 (28.09.1999) IN

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/22791 A2

(54) Title: CONTROLLED RELEASE COMPOSITIONS COMPRISING NIMESULIDE

(57) Abstract: A Controlled release pharmaceutical composition of Nimesulide comprising Nimesulide, as an active drug, one or more sustaining materials and pharmaceutical excipients formulated into a controlled release once-a-day oral dosage form.

Controlled Rel ase Compositions Comprising Nimesulide

The present invention relates to a controlled release composition of Nimesulide. The composition is related to a once-a-day dosage forms which are very useful in treatment of chronic diseases such as arthritis.

TECHNICAL BACKGROUND OF THE INVENTION

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) that also has antipyretic and analgesic properties. The compound is weakly acidic (pKa = 6.5) and differs from other NSAIDs in that its chemical structure contains a sulfonanilide moeity as the acidic group. (fig. 1) (Magni E, Nimesulide an overview, Drug Invest 1991; 3 Suppl. 2: 1-3).

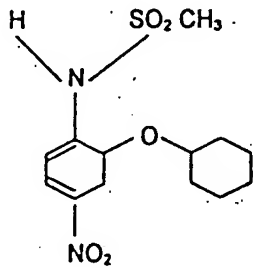

Fig. 1

The therapeutic effects of NSAIDs are largely the result of their ability to inhibit prostaglandin synthesis via inhibition of cyclo-oxygenase. Unfortunately, this effect is also responsible for the inhibition of gastroprotective prostaglandins, which leads to gastrointestinal intolerance.

In vitro, Nimesulide is a relatively weak inhibitor of prostaglandin synthesis and appears to exert its effects through a variety of mechanisms. (Magni E. The effect of nimesulide on prostanoid formation. Drugs 1993; 46 Suppl. 1:10-4.) Indeed, the mechanism of action of this drug is more complex than previously thought and may involve interference with the production/action of mediators other than prostaglandins such as enzymes, toxic oxygen derivatives, cytokines, platelet-activating factor (PAF) and histamine.

The anti-inflammatory, analgesic and antipyretic activities of Nimesulide, a non-steroidal anti-inflammatory drug (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials. Nimesulide has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as carrageenin-induced rat paw oedema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats. The analgesic potency in nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writhing test in rats, and acetic acid and acetycholine writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin and paracetamol (acetaminophen) in rats with yeast-induced fever.

Nimesulide is a relatively weak inhibitor of prostaglandin synthesis in vitro and appears to exert its effects through a variety of mechanisms including free-radical scavenging, effects on histamine release, the neutrophil mycloperoxidase pathway, bradykinin activity, tumour necrosis factor-α

release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet activating factor. Animal studies have suggested that Nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam and ibuprofen. Nimesulide appears to have little effect on renal prostaglandin synthesis in rats.

After oral administration of nimesulide 50 to 200 mg to healthy adult volunteers, peak serum concentrations of 1.98 to 9.85 mg/L are achieved within 1.22 to 3.17 hours. Compared with values obtained with oral drug administration, peak serum concentrations are slightly lower (2.14 to 2.32 mg/L) and are achieved more slowly (3 to 4.58 h) after rectal administration of nimesulide 100 and 200 mg. Oral drug absorption is nearly complete and concomitant administration of food may decrease the rate, but not the extent of absorption of nimesulide. The drug is extensively bound (99%) to plasma proteins and has an estimated apparent volume of distribution of 0.19 to 0.35 L/kg following oral administration.

In children, nimesulide suspension, granules and suppositories are more effective than placebo and are at least as effective as paracetamol, diclofenac, naproxen, lysine acetylsalicylate, mefenamic acid, ketoprofen and dipyrone in reducing in pain, inflammation and fever associated with respiratory tract infection, postoperative pain and musculoskeletal injury. Nimesulide has been well tolerated by both young and elderly adults and children in 2 large postmarketing surveillance surveys. As with other NSAIDs, the most common adverse effects are gastrointestinal disturbances

(epigastralgia, heartburn, nausea, diarrhoea and vomitings 5.1 to 8.5% of patients), dermatological reactions (rash, pruritus; 0.2 to 0.6%) and central nervous system effects (dizziness, somnolence, headache; 0.3 to 0.4%). Withdrawal rates associated with short term (up to 30 days) nimesulide treatment range from 1.1 to 2.2% in adult, elderly and paediatric patients.

Available data indicate that the gastrointestinal tolerability of nimesulide in adults and children is similar to that of other NSAIDs. The rate of endoscopically verified gastroduodenal irritation with nimesulide appears to be similar to that with placebo and diclofenac and less than that with indomethacin. The drug is well tolerated by most patients intolerant of aspirin and/or other NSAIDs and by patients with asthma.

The literature surveys shows that different dosage forms reported for nimesulide are tablets, granules, suppositories and suspension (Drugs 48 (3): 431-454, 1994) and lately our group has patented transdermal (US Pat. No. 5688829) and intramuscular injection (US Pat. No. 5716609) formulations. The reported dosage forms have to be administered twice-a-day based on biological half life of nimesulide. The usual oral/rectal dosage of nimesulide in adults is 100 to 200 mg twice daily, orally. For treatment of chronic diseases like arthritis the twice daily dosing regimen is difficult to comply with.

One approach to improve the possible non-compliance with the regimen is to develop controlled release dosage form for nimesulide The once-a-day dosage form is expected to significantly increase the dosing convenience and

patient compliance. However, controlled release once-a-day dosage form of nimesulide have not been reported so far.

Controlled release compositions for oral use in the form of matrix type monolithic tablets, beads, capsules and coated tablets are known. However poorly soluble drugs like nimesulide are known to give erratic and variable release under in-vivo conditions from such dosage forms.

One approach to formulate modified release dosage forms of NSAIDs is described in U.S. Pat. No. WO9912524, wherein a unit dosage form comprising two fractions (i) a first quick release fraction, and (ii) a second fraction containing coated delayed release multiple units is described. However, such dosage forms having different fractions and coated multiple units are difficult to prepare and very cost intensive. Moreover compression of such coated multiple units into tablets cause fracturing of the coat layer, thereby causing loss of reproducibility.

In U.S. Pat. No. 5788987 Busetti et al. describe a time-specific controlled release dosage form. Such dosage forms are designed to provide delayed release of the active ingredient rather than extended release. Such formulations are not suitable for day long management of the disease.

SUMMARY OF THE INVENTION

By expenditure of considerable intellectual effort and careful experimentation the inventors have discovered that nimesulide can be formulated into a controlled release once-a-day oral dosage form.

Such dosage forms provide extended release of nimesulide in-vivo when given once daily with reproducible bioavailability. Further the release of such dosage forms is not effected by pH changes in the gastrointestinal system.

The composition in accordance with present invention comprises a controlled release pharmaceutical composition of Nimesulide which comprises nimesulide as an active drug from 5% to 95% w/w of the composition in micronized form, one or more release sustaining materials from 2% to 95% w/w of the composition and pharmaceutical excipients from 0% to 90% w/w of the composition.

Preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 20% to 70% w/w of the composition, one or more sustaining materials from 5% to 65% w/w of the composition and pharmaceutical excipients from 10% to 70% w/w of the composition.

More preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 40% to 60% w/w of the composition, one or more sustaining materials from 8% to 20% w/w of the

composition and pharmaceutical excipients from 30% to 60% w/w of th composition.

DETAILED DESCRIPTION OF INVENTION

In accordance with the present invention there is disclosed a controlled release composition of Nimesulide.

The composition in accordance with present invention comprises a controlled release pharmaceutical composition of Nimesulide which comprises nimesulide as an active drug from 5% to 95% w/w of the composition, one or more sustaining materials from 2% to 95% w/w of the composition and pharmaceutical excipients from 0% to 90% w/w of the composition. In another aspect, such compositions contain nimesulide in micronized form having average particle size below 5 microns.

Preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 20% to 70% w/w of the composition, one or more sustaining materials from 5% to 65% w/w of the composition and pharmaceutical excipients from 10% to 70% w/w of the composition.

More preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 40% to 60% w/w of the composition, one or more sustaining materials from 8% to 20% w/w of the

composition and pharmaceutical excipients from 30% to 60% w/w of the composition.

In a preferred embodiment of the invention the composition consists of bilayer tablets wherein the active agent may be present in one or both layers. The bilayer tablets may be coated or uncoated. The coating may be semi-permeable type membrane. Further, the semi-permeable coat may have an orifice drilled through it on the drug layer side to provide passage for constant release of drug.

In another aspect of the invention the coating may be of microporous type through which the drug release takes place at constant rate.

In another aspect of the invention the bilayer tablet dosage form may have a first layer which gives fast release of the drug, and a second layer which gives extended release of the drug.

The first fast release layer comprises materials like disintegrants, fillers, rapidly soluble/dispersible excipients and wetting agents. The second extended release layer comprises sustaining polymers binders wetting agents and fillers.

The sustaining polymers preferably are hydrophilic in nature and present in a blend of fast and slow hydrating polymers.

The sustaining materials are selected from the group cellulose and cellulose derivatives, waxes, carbomers, polyalkylene polyols, polycarbophils, methacrylate acid derivatives, g latins, gums, polyethylene oxides.

The sustaining materials comprise materials which are non-toxic and pharmaceutically acceptable. These may be natural, semi-synthetic, synthetic or man-modified. Suitable materials include cellulose and cellulose derivatives like microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate , hydroxypropyl methylcellulose acetate succinate.

Polyethylene; Polyquaternium-1; Polyvinyl acetate (homopolymer); Polyvinyl acetate phthalate; Propylene glycol alginate; PVM/MA copolymer; PVP/ dimethiconylacrylate/polycarbamyl/polyglycolester;PVP/dimethylaminoethylm ethacrylate copolymer; PVP/dimethylaminoethylmethacrylate/polycarbamyl polyglycol ester; PVP/polycarbamyl polyglycol ester; PVP/ VA copolymer

Lanolin and lanolin derivatives, glyceryl monostearate, stearic acid, paraffins, beeswax, carnauba wax, Tribehenin.

Polyalkylene polyols like polyethylene glycols.

Gelatin and gelatin derivatives.

Alginates. Carbomers. Polycarbophils.

Methacrylic acid copolymers.

Carrageenans, pectins, chitosans, cyclodextrins, lecithins.

Natural and synthetic gums containing galactomannans like xanthan gum, tragacanth, acacia, agar, guar gum, etc.

Pharmaceutical excipients as used in the composition are selected from the group of excipients generally used by persons skilled in the art e.g. fillers, bulking agent, colourants, stabilizers, preservatives, lubricants, glidants, chelating agents and the like.

Preferably the composition also comprises release modifiers. Such release modifiers are selected from the groups wetting agents, solubilizers, surfactants, plasticizers, solvents, pore formers, pH modifiers and tonicity adjusting agents.

Suitable example of such ingredients include.:

Reaction products of natural and hydrogenated vegetable oils and ethylene glycol e.g. polyoxyethylene glycolated natural or hydrogenated castor oil such as those available under the trade name Cremophor.

Other suitable products include polyoxyethylene sorbitan fatty acid esters e.g. of the type available under the trade name TWEEN.

Polyoxyethylene fatty acid esters e.g. MYRJ and CETIOL HE.

Polyoxyethylene polyoxypropylene copolymers e.g. PLURONIC and Polyoxyethylene polyoxypropylene block copolymers e.g. POLOXAMER.

Dioctylsodiumsulfosuccinate, sodium lauryl sulphate.

Propylene glycol mono- and di- fatty acid esters e.g. MIGLYOL 840.

Bile salts e.g alkali metals salts e.g. sodium taurocholate.

Polyethylene glycols, propylene glycol, triacetin, diacetin, diethyl phthalate, dibutyl phthalate, castor oil, triethyl citrate dibutyl sebacate.

Sodium chloride, potassium chloride, lactose, mannitol, sucrose, sorbitol.

Sodium hydroxide, potassium hydroxide, sodium bicarbonate, sodium citrate, citric acid, hydrochloric acid, lactic acid, tartaric acid, malic acid.

The calculation of dose of nimesulide for once-a-day controlled release dosage form was done on the basis of its pharmacokinetic parameters using the following equation :

$$Dose = C_P \times V_d \times K_{el} \times T$$

C_P = Effective plasma concentration, 3.0 mg/L

V_d = Apparent Volume of distribution, 15.6 L

K_{el} = Elimination Rate constant, 0.166 h^{-1}

T = Desired Duration of action, 24 hrs

Based on the above equation the dose was calculated to be 207.0 mg.

The compositions of the present invention have another added advantage that once – a – day dosage form of Nimesulide may be combined with another suitable long – acting drug to have synergistic activity. The other

drug may be present in non-controlled release form. Such drugs may be selected from following categories :

(i) Antihistaminics e.g. Cetirizine Dihydrochloride.

(ii) Antispasmodics e.g. Pitofenone Hydrochloride, Hyoscine Hydrobromide.

(iii) Antiasthmatics e.g. Ketotifen, Salbutamol.

The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modifications without depending from the spirit and scope of the invention. All such modifications and variation are intended to be included within the scope of the invention as discuss in this specifications.

Example 1 Controlled release matrix tablet type

(i) Nimesulide (micronized)	-	200 mg
(ii) Lactose	-	73 mg
(iii) Hydroxypropylmethyl Cellulose	-	70 mg
(iv) Magnesium Stearate	-	3.5 mg
(v) Purified Talc	-	3.5 mg

Blend (i), (ii), (iii), (iv) and (v) after sifting through mesh no. 30 (BSS). Compress into tablets.

The results of Dissolution Release Profile of Nimesulide CR Tablets based on example 1 are given below :

Tabl 1

Time	Mean	SD
30 mins.	4.2	± 1.36
1 hr	7.9	± 1.02
2 hrs	16.4	± 1.74
3 hrs	25.8	± 1.28
4 hrs	34.2	± 1.71
6 hrs	50.8	± 2.44
8 hrs	65.9	± 1.86
10 hrs	74.9	± 0.97
12 hrs	85.8	± 2.34
14 hrs	93.5	± 2.49
16 hrs	96.7	± 2.16
18 hrs	97.1	± 1.08
19 hrs	98.8	± 1.32

The dissolution profile as given in table 1 of the nimesulide sustained release tablet should not be construed to limit the scope of the invention. Variations to the dissolution profile can be possible depending upon the dosage requirements without departing from the spirit of the invention.

Example 2 Extended release membrane diffusion controlled tablet type

(i) Nimesulide (micronized)	-	200 mg
(ii) Microcrystalline Cellulose	-	60 mg
(iii) Lactose	-	60 mg
(iv) Maize Starch	-	10 mg
(v) Purified Talc	-	3.5 mg
(vi) Ethyl Cellulose (As Aqueous Dispersion)	-	10 mg
(vii) Polyethylene Glycol	-	3.5 mg

Blend (i), (ii) and (iii) and granulate with starch paste and dry the granules. Sift through mesh no. 22 (BSS). Lubricate with Talc. Compress into tablets. Coat the tablets with Ethyl Cellulose using Polyethylene Glycol as a channel former.

Example 3 Sustained release bead type

(i) Non – Pareil Beads	-	347 mg
(ii) Nimesulide	-	200 mg
(iii) Mannitol	-	30 mg
(iv) Lactose	-	30 mg
(v) Polyvinyl Pyrrolidone	-	20 mg
(vi) Purified Talc	-	15 mg
(vii) Ethyl Cellulose	-	7 mg
(viii) Diethyl Phthalate	-	1.4 mg

Coat the non-pareil beads with blend of (ii), (iii) and (iv) using (v) as a binder in a conventional or fluidized bed coater. Talc may be dusted onto the beads. Final coating is given with Ethyl Cellulose using (viii) as plasticizer.

Example 4 Osmotically controlled constant release type device

Upper Layer

(i) Nimesulide (micronized)	-	200 mg
(ii) Sodium Hydroxide	-	15 mg
(iii) Lactose	-	34 mg
(iv) Sodium Chloride	-	30 mg

(v) Polyvinyl Pyrrolidone	-	6 mg
(vi) Polyethylene Oxide	-	1.5 mg
Lower Layer		
(vii) Polyethylene Oxide	-	22 mg
(viii) Hydroxypropylmethyl Cellulose	-	1.8 mg
(ix) Sodium Chloride	-	20 mg
(x) Dichloromethane	-	q.s (Lost in processing)
Semi-permeable Coat		
(xi) Cellulose Acetate	-	30 mg
(xii)Triacetin	-	1 mg
(xiii) Acetone	-	q.s (Lost in procesing)
(xiv) Water	-	q.s (Lost in processing)

Blend finely powdered (i), (ii), (iii), (iv) and (vi). Granulate with aqueous solution of (v). Granulate the blend of (vii) and (ix) with dispersion of (viii) in (x). Compress the two granulates into bilayer tablets and coat with the dispersion of (xii) and (xiii) in aqueous acetone. Finally, drill a hole in the drug layer (Upper layer) through which the drug is released in a controlled fashion due to osmotic pressure.

The results of Dissolution Release Profile of Nimesulide CR Tablets based on example 4 are given below :

Table 2

Time	Mean	SD
2 hours	5.16	± 0.53
4 hours	16.75	± 1.68
6 hours	34.90	± 2.26
8 hours	45.75	± 2.26

10 hours	56.00	± 4.36
12 hours	67.85	± 4.40
14 hours	79.16	± 5.03
14 hours	90.25	± 3.68
18 hours	101.16	± 3.53

Example 5 Coated capsule type

(i) Nimesulide (micronized)	-	200 mg
(ii) Microcrystalline Cellulose	-	88.4 mg
(iii) Lactose	-	70 mg
(iv) Polyvinyl Pyrrolidone	-	7 mg
(v) Magnesium Stearate	-	3.9 mg
(vi) Ethyl Cellulose	-	20 mg
(vii) Polyethylene Glycol	-	0.7 mg
(viii) Alcohol : Dichloromethane (1 : 2)	-	q.s (Lost in processing)
(ix) Empty Gelatin Capsule (Size '1')		

Blend (i), (ii), (iii), (iv) and (v) and fill into empty gelatin capsule size '1'. Coat the capsules with dispersion of (vi) and (vii) in (viii).

Example 6 pH dependent delayed release type

(i) Nimesulide (micronized)	-	100 mg
(ii) Microcrystalline Cellulose	-	150 mg
(iii) Lactose	-	76 mg
(iv) Polyoxyl 40 Hydrogenated Castor Oil	-	7 mg
(v) Polyvinyl Pyrrolidone	-	10 mg
(vi) Magnesium Stearate	-	3.5 mg

(vii) Purified Talc	-	3.5 mg
(viii) Cellulose Acetate Phthalate	-	28 mg
(ix) Diethyl Phthalate	-	2 mg
(x) Water	-	q.s (Lost in processing)
(xi) Alcohol : Dichloromethane (1:2)	-	q.s (Lost in processing)

Granulate the blend of (i), (ii) and (iii) with solution of (iv) and (v) in water. Blend the granules with (vi) and (vii). Compress into tablets. Coat with the dispersion of (viii) and (ix) in (xi).

Example 7 Timed release bead type

(i) Nimesulide (micronized)	100 mg	100 mg	100 mg
(ii) Microcrystalline Cellulose	200 mg	200 mg	200 mg
(iii) Lactose	50 mg	42 mg	35mg
(iv) Polyvinyl Pyrrolidone	10 mg	10 mg	10 mg
(v) Water	q.s	q.s	q.s
(vi) Ammonio Methacrylate Copolymer Type B (Eudragit RS)	10 mg	18 mg	25 mg
(vii) Diacetin	0.5 mg	0.5 mg	0.5 mg
(viii) Water : Acetone (1:9)	q.s	q.s	q.s

Procedure :

In this composition 3 types of beads are prepared which are coated with different amounts of (vi) to give a timed profile of the drug. Beads are prepared by blending and spheronizing (I), (ii) and (iii) jusing aqueous solution of (iv). The dried beads are coated with dispersion of (vi) and (vii) in (viii). The 3 different beads are blended together in a fixed ratio to obtain the required release profile.

Example 8 Nimesulide CR + Cetirizine Bilayered Tablets

Nimesulide Layer

(i) Nimesulide (micronized)	-	200 mg
(ii) Lactose	-	106.5 mg
(iii) Polyoxyl 40 Hydrogenated Castor Oil	-	2.0 mg
(iv) Hydroxypropylmethylcellulose	-	31.5 mg
(v) Magnesium Stearate	-	2.0 mg
(vi) Colloidal Silicon Dioxide	-	2.0 mg

Cetirizine Layer

(vi) Colloidal Silicon Dioxide	-	2.0 mg
(vii) Cetirizine Dihydrochloride	-	10.0 mg
(viii) Lactose	-	105.0 mg
(ix) Microcrystalline Cellulose	-	25.0 mg
(x) Starch	-	5.0 mg
(xi) Croscarmellose Sodium	-	3.0 mg
(xii) Magnesium Stearate	-	2.0 mg

Blend the components of the two layers separately and compress into bilayer tablets.

Example 9 Osmotically controll d constant release system

Active Layer

(i)	Nimesulide (micronized)	-	200.0 mg
(ii)	Polyethylene oxide	-	116.5 mg
(iii)	Hydroxypropylmethy cellulose	-	10.0 mg
(iv)	Sodium chloride	-	10.0 mg
(v)	Magnesium stearate	-	2.5 mg

Push layer

(vi)	Polyethylene oxide	-	140.0 mg
(vii)	Sodium chloride	-	50.0 mg
(viii)	Hydroxypropylmethy cellulose	-	9.5 mg
(ix)	Magnesium stearate	-	0.5 mg
(x)	Iron oxide red	-	1.0 mg

Functional coating

(xi)	Cellulose acetate	-	45.0 mg
(xii)	Polyethylene glycol	-	5.0 mg
(xiii)	Acetone	-	Lost in processing

Non-functional coating

(xiv)	Titanium dioxide	-	2.0 mg
(xv)	Hydroxypropylmethyl cellulose	-	6.0 mg
(xvi)	Purified Talc	-	2.0 mg
(xvii)	Polyethylene glycol – 400	-	2.0 mg
(xviii)	Isopropyl Alcohol	-	Lost in processing
(xix)	Dichloromethane	-	Lost in processing

Procedure : Blend (I), (ii), (iii), (iv) and (v) in a double cone blender. Separately blend (vi), (vii), (viii) (ix) and (x). Compress into bilayer tablet using a suitable compression machine. Coat the tablets with the dispersion of (xi) and (xii) in (xiii). The tablets are further coated with the dispersion of (xiv), (xv), (xvi), (xvii) in mixture of (xviii) and (xix).

Example 10 : Bilayer tablets having one fast release layer and one extended release layer

Fast Release layer

(i)	Nimesulide (micronized)	-	100.0 mg
(ii)	Lactose	-	151.5 mg
(iii)	Starch	-	37.6 mg
(iv)	Colloidal silicon Dioxide	-	11.0 mg
(v)	Povidone K-30	-	8.5 mg
(vi)	Docusate Sodium	-	6.8 mg
(vii)	Polysorbate 80	-	1.0 g
(viii)	Magnesium Stearate	-	1.6 mg
(ix)	Croscarmellose Sodium	-	22.0 mg
(x)	Water	-	Lost in processing

Extended Release Layer

(xi)	Nimesulide (micronized)	-	100.0 mg
(xii)	Lactose	-	200.0 mg
(xiii)	Hydroxypropylmethyl cellulose K100LV	-	23.0 mg
(xiv)	Hydroxypropylmethyl cellulose K4MCR	-	100.0 mg
(xv)	Povidone K-30	-	9.0 mg

(xvi)	Docusate Sodium	-	4.5 mg
(xvii)	Magnesium Stearate	-	4.5 mg
(xviii)	Colloidal Silicon Dioxide	-	4.5 mg
(xix)	Sodium Lauryl Sulphate	-	4.5 mg
(xx)	Isopropyl Alcohol	-	Lost in processing

Procedure :

Blend 1.: Blend (l), (ii), (iii) and (iv) and granulate with solution of (v) and (vi) in (x). Dry the granules and blend with (viii) and (ix).

Blend 2: Blend (ix), (xii), (xiii) and (xiv) and granulate with solution of (xv) and (xvi) in (xx). Dry the granules and mix with (xvii), (xviii) and (xix).
Compress into bilayer tablets using a suitable compression machine.

Example 11 : Bilayer tablets having one fast release layer containing drug in complexed form and one extended release layer

A	Fast Release layer		
(i)	Nimesulide (micronized)	-	100.0 mg
(ii)	B- cyclodextrin	-	400.0 mg
(iii)	Starch	-	70.0 mg
(vi)	Povidone K-30	-	7.5 mg
(v)	Croscarmellose Sodium	-	20.0 mg
(vi)	Magnesium Stearate	-	2.5 mg
B	Extended Release Layer		
(vii)	Nimesulide (micronized)	-	100.0 mg

(viii) Lactose	-	200.0 mg
(ix) Hydroxypropymethyl celluloses K100LV	-	230.0 mg
(x) Hydroxypropylmethyl cellulose K4MCR	-	100.0 mg
(xi) Povidone K-30	-	9.0 mg
(xii) Magnesium Stearate	-	4.5 mg
(xiii) Colloidal Silicon Dioxide	-	4.5 mg
(xiv) Docusate Sodium	-	4.5 mg

Procedure :

Layer-1

1. Mix (i) and (xii), co-mill under specific conditions favouring complexation using ball mill to prepare a complex.
2. Mix complex of step 1 with (iii) and granulate with a solution of (iv) in water
3. Dry the granules at 40^{O} 50^{O}C.
4. Size the granules & mix with (v) and (vi)

Layer – II

1. Mix (vii), (viii), (ix) and (x). Granulate with a solution of (xi) and (xiv).
2. Dry the granules at 40^{O}- 50^{O}C.
3. Size the granules & mix with (xii) and (xiii).
4. Compress the two layers into bilayered tablets using suitable compression machine.

We claim:

1. A Controlled release pharmaceutical composition of Nimesulide which comprises Nimesulide as an active drug upto 99% w/w of the composition, one or more release controlling materials from 0.1% to 99 % w/w of the composition and pharmaceutical excipients from 0% to 90% w/w of the composition.
2. A controlled release pharmaceutical composition of Nimesulide as claimed in claim 1 which comprises Nimesulide as an active drug from 20% to 70% w/w of the composition, one or more sustaining materials from 5% to 65% w/w of the composition and pharmaceutical excipients from 10% to 70% w/w of the composition.
3. A controlled release pharmaceutical composition of Nimesulide as claimed in claim 1 which comprises Nimesulide as an active drug from40% to 60% w/w of the composition, one or more sustaining materials from 8% to 20% w/w of the composition and pharmaceutical excipients from 30 % 60% w/w of the composition.
4. A controlled release pharmaceutical composition of Nimesulide as claimed in claim 1 to 3 wherein the sustaining materials are selected from the group cellulose and cellulose derivatives, waxes, carbomers, polyalkylene polyols, polycarbophils, methacrylate acid derivatives, gelatins, gums, polyethylene oxides and alike.
5. The composition as claimed in claim 1 which further comprises release modifiers.
6. A process for the manufacture of controlled release compositions of Nimesulide which comprises mixing together under conventional conditions of temperature and pressure- Nimesulide as an active drug upto 99% w/w of the composition, one or more release controlling sustaining materials from 0.1% to

99% w/w of the composition and pharmaceutical excipients 0% to 90% w/w of the composition.

7. A controlled release pharmaceutical composition of Nimesulide substantially as herein described with reference to foregoing description and the accompanying examples.
8. A process for the manufacture of controlled release compositions of Nim sulide substantially as herein described with reference to foregoing description and accompanying examples.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/22791 A3

(51) International Patent Classification[7]: A61K 9/20, 9/22

(21) International Application Number: PCT/IN00/00094

(22) International Filing Date:
27 September 2000 (27.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1297/DEL/99 28 September 1999 (28.09.1999) IN

(71) Applicant *(for all designated States except US)*: **PANACEA BIOTEC LIMITED** [IN/IN]; B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(71) Applicant and
(72) Inventor: **SINGH, Amarjit** [IN/IN]; Panacea Biotec Limited B-1 Extn./A-27, Mohan Co-operative Industrial Esta, te, Mathura Road, New Delhi 110 044 (IN).

(72) Inventor; and
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(74) Common Representative: **JAIN, Rajesh**; Panacea Biotec Limited, B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi 110 044 (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
31 January 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/22791 A3

(54) Title: CONTROLLED RELEASE COMPOSITIONS COMPRISING NIMESULIDE

(57) Abstract: A Controlled release pharmaceutical composition of Nimesulide comprising Nimesulide, as an active drug, one or more sustaining materials and pharmaceutical excipients formulated into a controlled release once-a-day oral dosage form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN00/00094

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US CL : 424/464, 468

According to International Patent Classification (IPC) or to both national classification and IPC

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U.S. : 424/464, 468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Physician's Desk Referenfce

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,666,928 A (YOUNG et al) 19 May 1987 (19.05.1987), column 9, lines 38-44, column 10, lines 64-66, column 13, lines 45-62.	1-8

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Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2001 (29.06.2001)	14 AUG 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Amy E. Pulliam Telephone No. (703) 308-1234

Form PCT/ISA/210 (second sheet) (July 1998)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

REVISED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/022791 A3

(51) International Patent Classification[7]: A61K 31/63, 9/20, A61P 29/00

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Published:
— *with international search report*

(88) Date of publication of the international search report:
31 January 2002
Date of publication of the revised international search report:
31 October 2002
Date of publication of the supplementary international search report:
15 May 2003

(15) Information about Corrections:
see PCT Gazette No. 20/2003 of 15 May 2003, Section II
Previous Correction:
see PCT Gazette No. 44/2002 of 31 October 2002, Section II

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SION

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 00/00094

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/63 A61K9/20 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 005 865 A (PANACEA BIOTEC LTD) 7 June 2000 (2000-06-07) page 5, line 6 - line 12 page 9 -page 10; example V	1-8
X	ES 2 129 010 A (GOLD OSCAR) 16 May 1999 (1999-05-16) page 3, line 27 - line 29 page 4; example 1	1-8

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Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2002	28/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Muller, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MANNA ET AL: "Design and evaluation of an oral controlled release microparticulate drug delivery system of nimesulide by ionotropic gelation technique and statistical optimization by factorial analysis" JOURNAL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, XP001064400 page 718; table 1	1,4-8
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		CN 1253776 A	24-05-2000
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ES 2129010 A	16-05-1999	ES 2129010 A1	16-05-1999
		IT MI972893 A1	02-07-1998
		PT 102095 A	31-07-1998
		US 6187343 B1	13-02-2001

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN00/00094

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Form PCT/ISA/210 (second sheet) (July 1998)